

Research on leukaemia cells surplus to diagnostic needs in children

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Abstract

The ability to improve diagnosis and refine prognosis in children with acute leukaemia is improving steadily. A growing number of tests can and are being performed on leukaemic cells. These include surface-marker analysis, DNA content, cytogenetics and studies of gene rearrangements. Increasingly large bone-marrow samples, now usually obtained under general anaesthesia, are required to make secure diagnoses.

Ethical issues arise from three major areas.

1) Current research on leukaemia cells requested by the Medical Research Council is considered by local research ethics committees, but parents are not regularly given detailed information about or asked specifically to consent to such research; 2) substantial quantities of excess cells are stored indefinitely. This archive of stored material is a valuable resource for research but there has been little consideration of the ethical issues which arise from this practice, and 3) there is a potential for pressure to obtain increasingly large samples.

'Creeping growth' in sample size is likely to continue unless ethics committees consider future research proposals in more detail. These issues deserve attention in order that worthwhile research and its publication are not impeded for want of ethical consideration. The implications extend beyond the field of childhood leukaemia.

Introduction

Investigations of leukaemia have long been at the leading edge of the interface between clinical value and pure research, and no more so than in children. Twenty years ago, a few drops of bone-marrow aspirated under local anaesthetic and spread onto glass slides provided ample material for all the available tests involved in making a diagnosis. With advances in special stains, chromosome studies, immunology and molecular biology the number of leukaemia cells and thus the volume of bone-marrow necessary to make, by modern standards, a secure diagnosis has increased substantially. The number of potentially clinically valuable investigations, as well

as more obscure tests of the leukaemia cell's genome, nucleus, cytoplasm and cell membrane has mushroomed. Some may prove to be clinically useful. Most will at least improve our understanding of the biology of the disease. A few will prove to have been no more than temporarily fashionable.

Currently, in order to obtain sufficient bone-marrow cells routinely to carry out all investigations of proven (or assumed) clinical value, several millilitres of bone marrow must be aspirated. This is not always easy, and if performed under local anaesthesia is distressful to most children. It has become standard practice in most paediatric oncology centres for bone-marrow sampling to be carried out under a short general anaesthetic. Up to 10 ml of bone-marrow and, in some centres, a trephine biopsy core may therefore be obtained without hurting the child. It is not possible to predict the cellularity of aspirated bone-marrow. In some cases even this volume of marrow may, because of unsuspected fibrosis of the marrow or other problems, contain less than the ideal number of leukaemia cells. However, in most cases substantial numbers of cells in excess of those required for diagnosis are obtained. It is this excess of cells from many, caused by the need to obtain enough from most, that provides 'research material'. In many cases the haematologist obtaining the diagnostic samples will be diagnostician, clinician, researcher and provider of material for research by others, a situation which lends itself to blurring of issues.

Ethical issues

There are three important areas in which ethical issues may arise; firstly, current research common to most paediatric oncology centres; secondly, the fate of cells which prove to be in excess of those required for current diagnostic and research purposes and, thirdly, the prospect of pressure to obtain larger samples.

1: RESEARCH COMMON TO MOST PAEDIATRIC ONCOLOGY CENTRES

Most children with acute leukaemia in the United Kingdom are now entered into therapy trials organised by the Medical Research Council (MRC).

Key words

Leukaemia; children; research.

One aspect of these trials is the investigation of features of the leukaemia cells which may be of diagnostic or prognostic benefit. Locally obtained results of tests of a wide range of biological features, including details of the pattern of certain cell-surface membrane molecules, quantity of DNA per cell and leukaemia-cell chromosome abnormalities are collected prospectively.

Each MRC trial has been considered by local research ethics committees (LRECs) and general approval of the whole trial given before individual centres enter patients. Ethical issues involved in carrying out this research will have been considered. It is accepted by haematologists that such research will not entail significant prolongation of the bone-marrow aspiration procedure beyond what is necessary to ensure adequate numbers of cells for the wide range of currently available diagnostic tests. The time taken to obtain sufficient bone-marrow will vary from case to case and will be affected by the ease with which marrow cells can be aspirated, the experience of the haematologist and logistical and other organisational variables in the operating theatre/anaesthetic room. However, no formal description of this research is routinely given to parents nor is specific consent to such research requested. It seems to be generally accepted that the research initiatives suggested by the MRC are so closely linked to established diagnostic practices and such an integral part of baseline data-collection that seeking specific consent would serve little useful purpose. Many haematologists will have considerable sympathy with this view. Without begging the question that this view is appropriate, this issue is probably not the most important or pressing of the three.

2: THE FATE OF CELLS IN EXCESS OF THOSE

REQUIRED FOR DIAGNOSIS AND MRC INVESTIGATIONS

Few centres automatically destroy such excess cells. Most will carry out one or two investigations, for example tests for cell-surface molecules, which are included in their local 'panel' of investigations although these are not necessarily of interest to the current MRC trial. Some centres have the facility to store, deep-frozen, intact leukaemia cells and/or DNA extracted from such cells. In addition the core of bone-marrow taken at diagnosis will have been fixed, embedded in paraffin wax or other medium, and sectioned for histological analysis. Most of the core is not consumed by initial sectioning. The 'block' (the embedded core) is retained indefinitely. The potential range of further investigations, even with currently available techniques, is great. New techniques, involving novel antibodies or probes for genes, continue to be described. This archive of stored, excess material, whether frozen cells, 'blocks' of fixed tissue or DNA extends back over more than ten years in several centres, continues to grow and provides an invaluable resource for research.

Traditionally, pathology and haematology departments have tended to view such material with a semi-proprietary eye, and together with interested clinicians and other scientists regularly go back to archives to test new antibodies and gene probes.

Society might be shocked, and justifiably so, if excess cells were routinely discarded without any consideration of contingency plans to conserve at least some of this tissue for future research. On the other hand, excess cells could be put to somewhat more controversial uses, such as establishing self-renewing cell-lines for commercial gain. These are extremes, but between them lie many solid, respectable and potentially clinically valuable uses of these archives.

The British Paediatric Association's guidelines for the ethical conduct of medical research involving children (1) highlight several aspects for consideration and it is worth examining potential research on such tissue in the same semi-structured way.

Children's interests

Concern for the subject's interests should prevail over those of society or science, particularly because other individuals (usually parents) may consent on children's behalf to such research. The potential benefit to the individual child of research on such stored cells is small, while that to science and future children may be great. On the other hand there is little against the child's interests beyond revealing in named children, who may have become long-term survivors, clinical uncertainties about their primary disease or potential predispositions to other pathology. Such revelations might affect, for example, future insurance policies or the state of mind of the individual in a harmful way. Anonymity might avoid these problems but arguably could be abandoned for unique, clinically important purposes.

Must the research involve children?

The short answer is 'yes'. There are too many aspects of the biology and clinical response of childhood leukaemia which differ markedly from adults to allow useful, valid conclusions to be drawn from work restricted to adults.

Potential benefit, harm and cost

Potential benefit to individual children of storing their own leukaemia cells is, as noted above, small. The most obvious potential benefits to future children lie in improving the accuracy of diagnosis and in refining our views about prognosis. Imprecise diagnoses lead to inappropriate treatment. Knowledge of prognosis can help in the management of future children and their families even if no alternative therapy is available. Much but not all of the research on cell-surface markers and genetic features is directly focused on obtaining such information.

Because this research is carried out on samples already and necessarily obtained for clinical

purposes, there is minimal (or arguably no) risk to the child from the research itself, beyond longer term problems should anonymity not be preserved.

Careful consideration should be given to the statistical power of such studies. Co-operation between centres, both in sharing data and carrying out investigations, already occurs. It may not be possible to forecast the financial implications of alternative therapeutic approaches which could be instituted as a result of such research, but experience has shown that the laboratory tests themselves, while perhaps expensive to carry out initially, soon become more economical, perhaps semi-automated or restricted to a few centres who do the work for others.

Role of local research ethics committees

MRC therapeutic trials are already considered by LRECs. However, most of the investigations contained in current trials were introduced, piecemeal, into the range of potentially valuable diagnostic or prognostic variables by individual centres as they became available. Only after some common ground was reached was the particular combination that is now used in these trials formally consolidated into a national trial. Little of the initial accrual of techniques was considered by LRECs, not least because the grey area which lies between 'proven clinical benefit' and 'research into potential clinical benefit' can be turned by relatively gentle mental contortions (and with the best of motives, too) by those closely involved into 'belief in clinical benefit'. LRECs are invaluable in helping to analyse such problems and in considering the issue of consent.

Consent

Some research which is based on tests (or material) already performed (or obtained) for therapeutic purposes may be permissible without consent because the research itself does not involve touching the child. When a child first presents with suspected leukaemia it may be impractical or meaningless to attempt immediately to obtain consent for the proposed research from distressed parents/guardians. Is a blanket consent, to any and all tests which may be, or later become, available to characterise the leukaemia, valid? With such broad terms of reference this question, and any consent, may be meaningless. Finally, the steady growth of new techniques and potentially testable hypotheses will create problems in informing parents/children about proposed research on previously stored cells. Because archives of material stretching back over several years already exist, much of this research will involve material from children who have become long-term survivors and who may not wish to have uncertainties revived or who have died and whose parents may have lost contact with the hospital, research laboratory and individuals involved in their care.

The issue of research on archival, stored material is growing in importance and merits attention.

Worthwhile research may be impeded, not least because it may become unpublishable for want of appropriate ethical consideration.

3: PRESSURE FOR INCREASED SAMPLE SIZE

It is unlikely that the amount of tissue required solely to make a secure diagnosis will need to be increased beyond that which is now used to carry out the currently available range of diagnostic investigations and research. There is still some excess for storage. The danger lies in the potential demand for additional research. Should such research require an increase in sample size there is a real prospect of significant prolongation of the bone-marrow sampling procedure. This would represent some increased risk (or discomfort if general anaesthesia is not used) to the child. When considering applications for future research LRECs will require guidance from those involved in such procedures – anaesthetists, haematologists and clinical paediatric oncologists – about the extent of that risk or discomfort. The full gamut of issues outlined in section 2 above will attain even greater importance. 'Creeping growth' in sample size is a natural and understandable phenomenon, driven on the whole by altruistic motives. The time may have come to draw a line under what has become, partly by default, standard practice and to examine more carefully any new proposals for research on freshly taken tissue samples. This issue is not yet urgently in need of attention, but the sooner this nettle is grasped the easier it will be to avoid crises.

Conclusions

This article has concentrated on childhood leukaemia because it is a field with which the author is familiar and because the problem of consent is even more taxing than in adults. The issue of information about and consent to current research on freshly taken cells has been partially hidden within overall consideration of therapeutic trials in childhood leukaemia. There has been little consideration of ethical issues involved in research on archival, stored material. Unless a line is drawn under current practice, 'creeping growth' in the size of tissue samples is likely to continue. The problems highlighted in this article will involve a wider range of tissue samples and patients than bone-marrow from children with leukaemia. LRECs and others need to consider these issues. At the head of the wave will be research involving children, not least because increasing numbers of scientific and medical journals will require specific statements from authors about ethical considerations.

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Reference

- (1) Ethics Advisory Committee of the British Paediatric Association. *Guidelines for the ethical conduct of medical*

research involving children. London: British Paediatric Association, 1992.

News and notes

A network on ethics and intellectual disability

Intellectual disability constitutes one of the fields in health care where ethical reflection is dearly needed, because of various social and political pressures. The aim of the network is to enable participants to share interests and concerns in this field and to communicate information on research programmes, policy developments and publications. It intends to stimulate exchange of views between scientists and ethicists from various religious and philosophical backgrounds and is not committed to any particular school of thought, nor does it advocate particular views on substantive or methodological issues.

A newsletter called *Ethics and Intellectual Disability* will be published twice a year, starting in winter 1995.

Members of the network can pass scientifically relevant information to the editor. The network participates in the scientific activities of the International Association of Bioethics. Co-ordinator of the network and editor of its newsletter is Prof Dr J S Reinders, Institute for Ethics, Free University, 1081 HV Amsterdam, the Netherlands.

If you are interested in becoming a member of the Network on Ethics and Intellectual Disability, please send your name and address to: IAB-Network Ethics and Intellectual Disability, Prof Dr J S Reinders, Free University, De Boelelaan 1105, 1081 HV Amsterdam, the Netherlands (fax: 20-4446635).

News and notes

Fellowship in clinical bioethics

The Department of Bioethics at the Cleveland Clinic Foundation invites applications for a one year Bioethics Fellowship residency, beginning 1 July 1995. The programme has an interdisciplinary focus and includes academic, clinical and research bioethics components. Each fellowship is tailored to meet individual strengths, needs and interests. Concentrations in medical sub-

specialties (for example, geriatrics, infectious disease) are available. Stipend and health care benefits are provided. Completed applications must be received by 15 January 1995. For information contact: Martin L Smith, STD, Department of Bioethics, P-31 Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA. Telephone: (216) 444-8720.